Acute respiratory distress syndrome in wartime military burns: Application of the Berlin criteria

Slava M. Belenkiy, MD, Allison R. Buel, DO, Jeremy W. Cannon, MD, Christy R. Sine, MD, James K. Aden, PhD, Jonathan L. Henderson, MD, Nehemiah T. Liu, MS, Jonathan B. Lundy, MD, Evan M. Renz, MD, Andriy I. Batchinsky, MD, Leopoldo C. Cancio, MD, *and* **Kevin K. Chung, MD,** *San Antonio, Texas*

BACKGROUND: Acute respiratory distress syndrome (ARDS) prevalence and related outcomes in burned military casualties from Iraq and Afghanistan have not been described previously. The objective of this article was to report ARDS prevalence and its associated in-hospital mortality in military burn patients.

METHODS: Demographic and physiologic data were collected retrospectively on mechanically ventilated military casualties admitted to our burn intensive care unit from January 2003 to December 2011. Patients with ARDS were identified in accordance with the new Berlin definition of ARDS. Subjects were categorized as having mild, moderate, or severe ARDS. Multivariate logistic regression identified independent risk factors for developing moderate-to-severe ARDS. The main outcome measure was the prevalence of ARDS in a cohort of patients burned as a result of recent combat operations.

RESULTS: A total of 876 burned military casualties presented during the study period, of whom 291 (33.2%) required mechanical ventilation. Prevalence of ARDS in this cohort was 32.6%, with a crude overall mortality of 16.5%. Mortality increased significantly with ARDS severity: mild (11.1%), moderate (36.1%), and severe (43.8%) compared with no ARDS (8.7%) ($p < 0.001$). Predictors for the development of moderate or severe ARDS were inhalation injury (odds ratio [OR], 1.90; 95% confidence interval [CI], 1.01–3.54; $p = 0.046$), Injury Severity Score (ISS) (OR, 1.04; 95% CI, 1.01–1.07; $p = 0.0021$), pneumonia (OR, 198; 95% CI, 1.07–3.66; $p = 0.03$), and transfusion of fresh frozen plasma (OR, 1.32; 95% CI, 1.01–1.72; $p = 0.04$). Size of burn was associated with moderate or severe ARDS by univariate analysis but was not an independent predictor of ARDS by multivariate logistic regression ($p > 0.05$). Age, size of burn, and moderate or severe ARDS were independent predictors of mortality.

CONCLUSION: In this cohort of military casualties with thermal injuries, nearly a third required mechanical ventilation; of those, nearly one third developed ARDS, and nearly one third of patients with ARDS did not survive. Moderate and severe ARDS increased the odds of death by more than fourfold and ninefold, respectively. (*J Trauma Acute Care Surg*. 2014;76: 821–827.

LEVEL OF EVIDENCE: Epidemiologic/prognostic study, level III.

KEY WORDS: Mechanical ventilation; adult respiratory distress syndrome; the Berlin definition; combat casualty care; burns.

Thermal injuries are common in a combat environment and represent approximately 3% to 10% of casualties.[1–4] Historically, thermal injuries have been associated with the development of acute respiratory distress syndrome (ARDS) in 2% to 17% of patients,[5–7] whereas 40% to 54% of burn patients requiring mechanical ventilation (MV) go on to develop ARDS.[6,8,9] Previously reported risk factors for the development of ARDS were age,[5] sepsis, and delayed resuscitation,[6] whereas the association between ARDS and inhalation injury (II) is unclear. Some studies found no association,[5,6] while others have reported II as an important risk factor for ARDS.[10,11] The diagnosis of ARDS is associated with increased mortality in burn patients, ranging from 14% to 42%.[5,6] A recent meta-analysis by Zambon and Vincent[12] reported an overall pooled mortality of 43% for a mixed population of patients with acute lung injury (ALI)/ARDS between the periods of 1994 and 2006.

In 2012, a new definition of ARDS was proposed, termed the Berlin definition (Supplemental Digital Content 1, http://links.lww.com/TA/A367).[13] It redefined three separate categories of ARDS based on the degree of hypoxia measured as the ratio of a partial pressure of arterial oxygen (Pa_{O_2}) to a fraction of inspired oxygen (FI_{O_2}) (PFR). These new categories were (1) mild (200 mm Hg < PFR ≤ 300 mm Hg), (2) moderate (100 mm Hg < PFR ≤ 200 mm Hg), and (3) severe (PFR ≤ 100 mm Hg). Also new, the definition clarified the timing of the "acute onset" of the respiratory failure, which specifically should be within 7 days of a known clinical event. In addition, it added a minimal requirement of at least 5 cm H_2O of a positive end expiratory pressure (PEEP) or continuous positive airway pressure for a condition to be classified as ARDS of any severity. Finally,

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From the San Antonio Military Medical Center (S.M.B., A.R.B., J.W.C., C.R.S., and J.L.H.); and US Army Institute of Surgical Research (S.M.B., J.K.A., J.B.L., E.M.R., A.I.B., L.C.C., K.K.C., and N.T.L.), Fort Sam Houston, San Antonio, Texas; and Uniformed Services University of the Health Sciences (J.W.C., E.M.R., and K.K.C.), Bethesda, Maryland.

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Address for reprints: Kevin K. Chung, MD, US Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, San Antonio, TX 78234-6315; email: kevin.k.chung.mil@mail.mil.

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clarifications were made to the radiologic imaging criteria describing pulmonary edema and imaging modality.[13] The longstanding American-European Consensus Conference (AECC) definition[14] classified ARDS as a respiratory failure with a PFR ≤ 200 mm Hg and uses a separate, less severe category (ALI), defined as 200 mm Hg < PFR ≤ 300 mm Hg. According to this older classification, radiologic features were also criteria as was the presence of noncardiogenic pulmonary edema.

The main distinction between the two definitions is a new "severe ARDS" category, which encompasses critically ill patients with reported mortality rates as high as 45% and the use of PEEP as an aspect of the definition.[13] In addition, by eliminating the ALI category and renaming it "mild ARDS," the Berlin definition recognizes that it is a milder spectrum of the disease that still carries a high mortality rate (as high as 27%).[15,16] Since publication of the new definition, some authors have proposed a simplified version, which combines mild and moderate ARDS as a single category.[15] Their meta-analysis indicated that at the time of the diagnosis of ARDS, mild and moderate categories had a similar odds ratio (OR) for mortality. However, after 24 hours, all three categories varied significantly in mortaliy.[16] The severe category was associated with the highest mortality. Therefore, the main strength of the Berlin definition is that it improves risk stratification.

In summary, we believe that application of the Berlin definition of ARDS in burned military casualties provides better risk stratification and therefore permits earlier recognition of this deadly syndrome, which may lead to earlier and more aggressive use of adjunctive therapies with resultant improved outcomes.[17,18]

We undertook this study to answer the following questions. (1) What is the prevalence of ARDS, based on the Berlin definition, among the military burn casualties? (2) What are the risk factors for developing ARDS in that patient population? (3) Is ARDS an independent risk factor for death in military casualties with burns?

PATIENTS AND METHODS

Clinical Setting

The US Army Institute of Surgical Research (USAISR) burn center includes a 16-bed burn intensive care unit (BICU) located in a tertiary military teaching hospital and Level I trauma center. It is the only facility in the US Department of Defense that provides burn care to active-duty military personnel worldwide. The USAISR Burn Center is a Level V facility within the chain of evacuation and the principal destination for all US service members burned during combat operations. The facility is equipped with a dedicated burn flight team, which in conjunction with the US Air Force aeromedical assets is capable of providing transcontinental evacuations of severely burned casualties to the USAISR BICU for further care.[19] To assist with prehospital management of the burn casualties, clinical practice guidelines were developed.[20] In addition, clinical practice guidelines contain burn flow sheets that are designed to assist with burn resuscitation and to standardize care.[21] Upon arrival

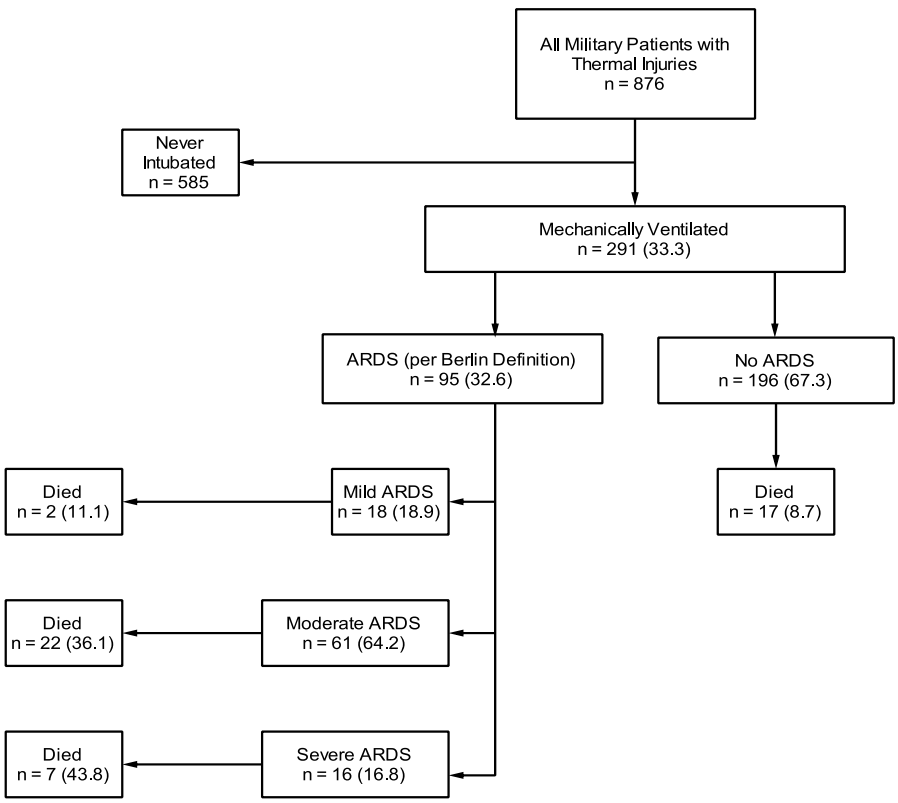

Figure 1. Consort diagram of the study population. Values are n (%) unless indicated otherwise.

TABLE 1. Study Cohort Demographics (n = 291)

Characteristics	Mean (SD) or n (%)
Age, y	26.3 (7.2)
Sex	
Male	284 (7.6)
Female	7 (2.4)
Race/ethnicity	
White	165 (56.7)
Black	26 (8.9)
Hispanic	26 (8.9)
Other or unknown	74 (25.4)
%TBS	33.7 (23.7)
%FTB	25.5 (23.9)
Mechanism of thermal injury	
Flame	39 (13.4)
Electric	5 (1.7)
Steam	4 (1.4)
Noncombat trauma	2 (0.2)
Combat-related trauma	241 (82.8)
II	128 (44.0)
ISS	25.8 (14.1)

FTB: full-thickness burn.

to the USAISR BICU, all patients underwent a fiber-optic bronchoscopy, and presence of II was confirmed by a burn attending physician. All patients underwent their initial excision and grafting procedure within 3 days of arrival. The USAISR BICU uses electronic medical records.

Study Design and Participants

After obtaining approval from the US Army Medical Research and Materiel Command Institutional Review Board and ensuring full compliance of the protocol with the US Department of Health and Human Services' Health Insurance Portability and Accountability Act, we evaluated all burned combat casualties admitted to the BICU from January 2003 through December 2011. We then specifically evaluated all such patients managed on MV. Data extracted from the electronic medical records included age, sex, race, mechanism of injury, timing of the injury and admission, size of the burn or a percentage of the total body surface area (%TBS) burned, percentage of full-thickness burn, presence of II, Injury Severity Score (ISS), pneumonia, length of ICU and hospital stay, and survival. Mechanism of injury was determined to be "combat-related trauma" if the patient was exposed to an explosion of any type with concomitant trauma. Ventilation parameters including ventilation mode, duration of MV support, arterial blood gas values, fraction of inspired oxygen (FIO_2), peak inspiratory pressures, PEEP, and tidal volume were recorded when available. In addition, we recorded the total volume of resuscitation fluid in the first 24 hours postburn period, development of acute kidney injury (AKI) graded in accordance with the criteria of the Acute Kidney Injury Network (AKIN),[22] and blood products transfused before the diagnosis of ARDS. To identify patients from this cohort meeting diagnostic criteria for ARDS based on the Berlin definition, one of the three pulmonary and critical care fellows (C.R.S., A.R.B., J.L.H.) reviewed all the records. Arterial blood gas values on the day of ARDS diagnosis were used to calculate PFR. Radiologic criteria were determined based on chest x-ray radiology reports. Heart failure or hydrostatic edema caused by fluid overload was ruled out based on echocardiography reports (subject to availability) or the evidence of improvement in pulmonary infiltrates with diuresis as the only intervention as documented in the daily progress notes. All patients that met the criteria for ARDS underwent a second chart review by a different pulmonary and critical care fellow (C.R.S., A.R.B.). In cases of disagreement between the two fellows, a third reviewer (K.K.C.) adjudicated. For patients with ARDS, timing between injury and the diagnosis of ARDS was determined and recorded.

Statistical Analysis

Continuous variables were compared using analysis of variance, and discrete variables were compared using χ^2 test. Missing data were excluded from the analysis. All relevant factors were analyzed to determine whether they were significantly associated with ARDS based on the Berlin criteria. Multiple logistic regression was then performed to predict moderate-to-severe ARDS. Only factors that were significantly associated with ARDS in the univariate analysis were considered. Factors were removed one by one via backward elimination until only factors with a $p < 0.10$ were left in the final model. Statistical significance was defined as a $p < 0.05$. Similarly, multiple logistic regression with sequential stepwise selection was performed to predict mortality. The following factors were considered: age, II, and TBS because of previously reported association with increased mortality.[1] In addition, transfusion of fresh frozen plasma (FFP), AKI, and the Berlin categories of ARDS were included. All statistical analysis was completed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 876 burned combat casualties were admitted to our Level V combat military hospital during the study period, of whom 291 (33.2%) were admitted to the BICU and required MV (Fig. 1). Table 1 illustrates baseline demographic and clinical data for this cohort. The majority of those injuries were caused by combat-related trauma 241 (82.8%) with

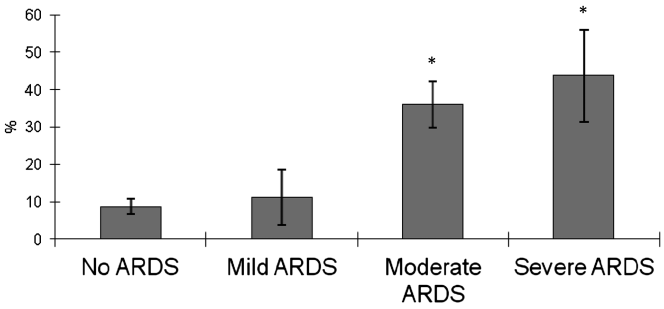

Figure 2. Overall mortality (%) in mechanically ventilated patients with thermal injury based on ARDS category. *Bars* indicate ±SD; *Dunnett's post hoc test $p < 0.05$ when compared with no ARDS; the difference between moderate and severe ARDS was insignificant ($p > 0.05$).

presumed exposure to blast. The mean (SD) duration MV support was 15.6 (24.8) days, while mean (SD) ICU stay was 42.8 (205.5) days. Our subjects were young (mean [SD] age, 26.3 [7.2] years), and 97.6% were male. MV patients had a high prevalence of II (44%). Overall mortality in the MV cohort was 16.5% (Table 3). Nearly one third of MV patients (32.6%) developed ARDS. Based on the Berlin definition, 18 (6.1%) of the MV patients had mild, 61 (21.0%) had moderate, and 16 (5.5%) had severe ARDS. Mean (SD) time to onset of ARDS was 12.4 (27.2) days from initial burn injury. Of the patients with ARDS, 32.6% died. Mortality in ARDS increased significantly with escalating severity category (8.7% no ARDS vs.11.1% mild; 36.1% moderate; and 43.8% severe; $p < 0.001$) (Fig. 2). Table 2 illustrates univariate comparisons that were made for the subsets of ARDS categories.

Variables that were significantly associated with ARDS in the univariate analysis were entered into a multivariate logistic model to predict moderate or severe ARDS. The following variables were found to be independently associated with moderate or severe ARDS in this population: II (OR, 1.90; 95% confidence interval [CI], 1.01–3.54; $p = 0.046$), ISS (OR, 1.04; 95% CI, 1.01–1.07; $p = 0.0021$), pneumonia (OR, 198; 95% CI, 1.07–3.66; $p = 0.03$) and FFP transfusion (OR, 1.32; 95% CI, 1.01–1.72; $p = 0.04$) (Table 3). The burn size (%TBS), AKI, first 24-hour fluids, and mechanism of injury were not found to be predictive of moderate or severe ARDS ($p > 0.05$). In addition, stepwise multivariate regression was constructed to predict death in this patient population. The following variables were identified as independent predictors of mortality in this cohort: age, burn size (%TBS), and moderate or severe ARDS. II, FFP transfusion, and mild ARDS were not predictive of death ($p > 0.05$) (Table 4).

DISCUSSION

To our knowledge, our study is the first to describe the prevalence of ARDS among burned military casualties. It is also the first to use the Berlin criteria for diagnosing ARDS in the military population. The Berlin definition was created to simplify and improve the recognition of the syndrome and to better risk-stratify the patients based on severity of the disease. Both of these aims fit our military needs well, prompting us to evaluate the applicability of this new definition to our military burn casualties.

Overall, we found that nearly one third (33.2%) of evacuated military burn casualties required MV. Of those who required MV, the prevalence of ARDS was 32.6%, with an associated mortality of 32.6%. Our MV data seem to be similar to the results previously described by Dancey et al.,[5] who reported that among 469 burn admissions, 26.9% required MV; however, their prevalence of ARDS (defined by AECC) was higher at 53.6%, with an associated mortality of 41.8%. It is important to point out that the study of Dancey et al. was performed between 1991 and 1995, before the wide adoption of the principle of lung protective ventilation,[14] and that the study's patient population was much older: the mean (SD) age of the patients was 46.9 (17.9) years[5] compared with 26.3 (7.2) in our population. Overall, our mortality rate of 16.5% in a cohort of mechanically ventilated burn patients seems

TABLE 2. Univariate Analysis of Variables Associated with the Development of ARDS and Associated Outcomes

Variables	All MV Patients (n = 291)	No ARDS (n = 196)	Mild ARDS (n = 18)	Moderate ARDS (n = 61)	Severe ARDS (n = 16)	p
Age, mean (SD), y	26.3 (7.2)	25.6 (6.2)	27.9.1 (8.5)	27.5 (9.2)	26.7 (8.4)	0.19
Female, n (%)	7 (2.4)	5 (2.6)	0	2 (3.3)	0	0.79
%TBS, mean (SD)	33.7 (23.7)	30.0 (21.7)	41.7 (25.7)	42.2 (25.9)*	37.4 (27.1)	0.002
%FTB	25.5 (23.9)	22.0 (22.1)	30.8 (26.3)	34.0 (26.5)*	29.3 (25.8)	0.004
II, n (%)	128 (44.0)	76 (38.8)	7 (38.9)	37 (60.7)	8 (50.0)	0.010
ISS, mean (SD)	25.8 (14.1)	23.4 (13.2)	30.6 (16.3)	32.2 (15.7*)	26.7 (8.0)	<0.001
Initial 24-h fluid resuscitation, mean (SD), L	17.6 (12.9)	16.4 (13.6)	18.0 (15.6)	20.0 (10.2)	21.1 (14.1)	0.65
Timing to ARDS, mean (SD), d	12.4 (27.2)	NA	8.7 (10.2)	8.6 (15.3)	16.4 (26.2)	0.81
Blood products, mean (SD)						
PRBC, U	3.3 (8.8)	3.2 (9.1)	3.6 (8.8)	4.1 (8.7)	1.4 (3.5)	0.74
FFP, U	1.6 (4.9)	0.9 (3.3)	3.8 (7.9)	3.0 (6.5)	2.9 (7.7)	0.003
PLT, packs	0.4 (1.7)	0.2 (1.3)	0.7 (1.7)	0.8 (2.6)	0.6 (2.3)	0.065
AKIN ≥ 1, n (%)	206 (70.1)	136 (69.4)	14 (77.8)	44 (72.1)	12 (75.0)	<0.001
Pneumonia, n (%)	156 (53.6)	87 (44.4)	11 (61.1)	46 (75.4)	12 (75.0)	<0.001
Outcomes						
Duration of MV, mean (SD), d	15.6 (24.8)	11.3 (21.1)	19.2 (33.5)	27.6 (30.2)*	17.3 (19.5)	<0.001
ICU LOS, mean (SD), d	42.8 (205.5)	24.3 (32.4)	49.1 (97.3)	103.1 (439.2)*	32.5 (39.6)	0.075
Hospital LOS, mean (SD), d	58.7 (64.2)	75.2 (110.6)	80.0 (110.3)	68.0 (74.6)	55.6 (90.2)	0.35
Mortality, n (%)	48 (16.5)	17 (8.7)	2 (11.1)	22 (36.1)	7 (43.8)	<0.001

*Dunnett's post hoc test $p < 0.05$.
Values are n (%) unless indicated otherwise.
FTB, full-thickness burn; LOS, length of stay; PLT, platelets; PRBC, packed red blood cells; NA, not applicable.

TABLE 3. Significant Predictors for the Development of Moderate and Severe ARDS

Multivariable Predictor	OR Point Estimate	95% Wald Confidence Limits	*p*
II	1.90	1.01–3.54	0.046
ISS	1.04	1.01–1.07	0.0021
Pneumonia	1.98	1.07–3.66	0.03
PRBC, U	0.95	0.88–1.01	0.09
FFP, U	1.32	1.01–1.72	0.04

PRBC: packed red blood cells.

comparable with 13.9% (ranging from 4.0% to 28.3%), as previously reported in a systematic review.[23]

The Berlin criteria seem to be most helpful in stratifying patients into the moderate and severe categories as the odds of death increased by more than fourfold and ninefold, respectively, when compared with those with no ARDS. In contrast, mortality in the mild ARDS category was no different from those without. Perhaps, our results provides better fidelity than the work by Dancey at al.,[5] which suggested that diagnosis of ARDS based on AECC definition did not result in increased mortality in burn patients. Our results confirm that a more stratified approach to the diagnosis of ARDS remains clinically relevant, with mortality rates closely tied to the development and the severity of the disease, even in a young population. Others have reported that an increase in mortality rates is directly related to the severity of ARDS.[13]

Given the high mortality rates in the moderate and severe categories, it is important to identify the risk factors associated with their development. In our population, we identified ISSs and FFP transfusions as the only two independent predictors of moderate or severe ARDS. These can be considered important surrogate markers that signal the presence of significant concomitant trauma and is consistent with recent finding in nonburn military casualties.[24] Interestingly, the subgroup of patients categorized as having combat-related trauma did not experience a higher rate of ARDS. This is likely caused by the fact that the cohort involved a wide range of trauma severity with variable exposure to blast. The independent link between FFP and ARDS in this population may go beyond a simple association. Previous reports have suggested a strong link between the use of FFP and the development of ALI (AECC definition) in severely injured patients.[25,26] Similar results were observed in combat settings, where a volume of transfused FFP was independently associated with ALI and ARDS.[24,27] Our present results are aligned with these earlier findings.

In our analysis, both the presence of II and pneumonia independently increased the odds of moderate or severe ARDS. A definitive relationship between ARDS and II is not clear in the literature. Several studies found no link between ARDS and II,[5,6] whereas others deemed it to be a significant factor.[10,11] It is important to emphasize that the association between pneumonia and ARDS is just an association and does not necessarily indicate a cause-and-effect relationship. Finally, resuscitation fluid volume was not significantly associated with the development of ARDS in our population. This may also be a result of relatively small sample size, although our group has previously reported that different fluid resuscitation strategies did not result in a significant difference in the prevalence of early ALI/ARDS.[28]

While an independent relationship between AKI and mortality is well described in burns,[29] this was not clear in this data set. AKI was associated with ARDS by univariate analysis. However, AKI (AKIN stage ≥ 1[22]) was not predictive of death in the logistic regression model. Perhaps, further investigation to establish the relationship between ARDS and AKI using a larger data set should be undertaken. Similarly, although ISS was associated with ARDS and was an independent predictor for moderate or severe ARDS, it was not predictive of death in the multivariate regression model. This indicates that although concomitant trauma is an important factor that contributes to the development of ARDS, other factors (such as TBS and age) contribute to death by a greater degree.

Given that the development of moderate or severe ARDS is still associated with a high mortality despite optimal ventilator support and other rescue strategies as previously described,[8,9] perhaps, alternative adjunctive therapies, such as minimally invasive extracorporeal life support systems, should be explored in this population. This may only be applicable, however, in patients with either isolated II[17] or in burn patients with minimal risk for bleeding.[18]

Inherent limitations exist given the retrospective nature of this study. II was a dichotomous variable and not graded based on severity. It is possible that we may have detected a relationship between severe II and ARDS. Moreover, the diagnosis of ARDS is difficult to make with certainty through a simple chart review. We tried our best to overcome this limitation by applying a structured adjudication process as we used the Berlin diagnostic criteria to categorize our patients. Still, there is a small chance that these patients could have been mischaracterized. Another limitation may be that our study only singled out combat burn casualties, which may not be reflective of the civilian population and thus not generalizable. We believe that valuable insight can be gained by this unique population, many of whom had concomitant blast-related trauma. Finally, the vast majority of our subjects were young previously healthy males, potentially skewing the mortality data.

The strength of the Berlin ARDS definition comes from the following: (1) it eliminates a separate entity—ALI, instead

TABLE 4. Significant Predictors of Death in Combat Burned Patients

Multivariable Predictor	OR Point Estimate	95% Wald Confidence Limits	*p*
Age, y	1.08	1.02–1.13	0.005
II	1.19	0.49–2.92	0.70
ISS	2.61	0.99–1.07	0.20
TBS	1.05	1.04–1.07	<0.0001
AKIN score ≥ 1	2.61	0.79–8.62	0.12
Mild ARDS	0.56	0.91–3.48	0.54
Moderate ARDS	4.42	1.79–10.90	0.001
Severe ARDS	9.52	2.43–37.28	0.001

reclassifying it as a milder spectrum of the same syndrome; (2) it defines a new category of severe ARDS, which carries the highest mortality rate; and (3) it defines specific timing of an acute onset. These provisions may increase recognition of the disease and improve risk stratification. Our analysis of the burn military casualties allowed us to further risk-stratify a previous planning assumption: that up to 10% of all wartime casualties will experience thermal injuries;[2] in addition, approximately one third of burn combat casualties will require MV; approximately one third of those will develop ARDS, and approximately one third of patients with ARDS will not survive.

CONCLUSION

More than one third of military burn patients who require MV develop ARDS. Moderate and severe ARDS based on the Berlin criteria increases the odds of death by more than fourfold and ninefold, respectively, compared with no ARDS. The Berlin criteria are clinically helpful in risk stratifying patients in the moderate and severe categories.

AUTHORSHIP

L.C.C. and K.K.C. contributed to the original conception of the study. S.M.B., A.R.B., C.R.S., and J.L.H. performed the data extraction and management. S.M.B., A.R.B., C.R.S, J.K.A., N.T.L., and K.K.C. performed the data analysis and created the charts and figures. S.M.B., J.W.C., A.R.B., and K.K.C. wrote the manuscript. J.W.C., E.M.R., A.I.B., J.B.L., and L.C.C. critically reviewed the manuscript. K.K.C. directed the study team and approved the final manuscript.

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DISCLOSURE

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